In order to provide the most up-to-date and efficacious care to their patients, oncologists must be aware of the emerging pharmacotherapeutic agents and therapies assessed in clinical trials. The trials reviewed here evaluated investigational agents and regimens for the treatment of ovarian, breast, lung, pancreatic, colorectal, and renal cancer. The purpose, methods, results, and conclusions of each study are reported, and managed care implications are presented.

**Title:** Phase III trial of infusional fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) compared with infusional fluorouracil, leucovorin, and irinotecan (FOLFIRI) as first-line treatment for metastatic colorectal cancer: the Grupo Oncologico Nord Ovest.

**Authors:** Falcone A, Ricci S, Brunetti I, et al.


**Purpose:** The present treatment for metastatic colon cancer consists of a three drug regimen of fluorouracil, leucovorin and irinotecan (FOLFIRI) or oxaliplatin (FOLFOX) +/- a targeted therapy agent. Results have shown an improved progression-free survival (PFS) and overall survival (OS) when compared to fluorouracil and leucovorin alone. This study compares the four drugs in combination (FOLFOXIRI) to the standard three drug combination (FOLFIRI).

**Methods:** This phase 3 trial enrolled patients aged 18 to 75 with unresectable, measurable, metastatic disease of the colon or rectum with a good performance status and adequate renal, hepatic and hematologic function. Adjuvant therapy with fluoropyrimidine-based therapy was allowed as long as it was completed at least 6 months prior to entry on the study. Previous treatment with irinotecan or oxaliplatin was not allowed. FOLFOX chemotherapy consisted of irinotecan 180 mg/m² over 1 hour on day 1 followed by leucovorin 100 mg/m² over 2 hours, 5-FU 400 mg/m² as an IV bolus followed by a 600 mg/m² infusion over 22 hours. The leucovorin and 5-FU portions of the therapy were repeated on day 2. FOLFOXIRI consisted of irinotecan 165 mg/m² over 1 hour on day 1 followed by oxaliplatin 85 mg/m² over 2 hours, leucovorin 200 mg/m² over 2 hours and 5-FU 3200 mg/m² as a continuous infusion over 48 hours. Both regimens were repeated every 2 weeks. The primary end point of the study was response rate (RR). Secondary end points included PFS, OS and safety.

**Results:** A total of 244 patients were randomly assigned to receive either FOLFIRI (n=122) or FOLFOXIRI (n=122). Response rates were 34% for the FOLFIRI arm versus 60% for the FOLFOXIRI arm (P<0.001) when reviewed by an external panel.
PFS and OS were both significantly improved with the four drug regimen (median PFS, 9.8 vs 6.9 months, P=0.0006; median OS, 22.6 vs 16.7 months, P=0.032). As expected the toxicity of the four drug treatment arm was more severe particularly grade 2 and 3 peripheral neuropathy (19% vs 0%, P<0.001) and grade 3 and 4 neutropenia (50% vs 28%, P<0.001). No significant difference was noted in the incidence of febrile neutropenia or diarrhea.

Conclusions: The FOLFOXIRI regimen improves RR, PFS and OS with increased, but manageable toxicity in patients with metastatic colorectal cancer with favorable prognostic characteristics. Additional studies combining this regimen with targeted therapies and in the neoadjuvant setting are warranted.

Title: Phase III trial of capecitabine plus oxaliplatin as adjuvant therapy for stage III colon cancer: a planned safety analysis in 1,864 patients.

Authors: Schmoll H-J, Cartwright T, Tabernero J, et al.


Purpose: To report the results of the planned safety analysis comparing oral capecitabine and intravenous oxaliplatin (XELOX) to bolus fluorouracil/leucovorin (FU/LV) in adjuvant therapy for stage III colon cancer.

Methods: Patients ≥18 years of age with stage III colon cancer were assigned to a treatment arm within 8 weeks following curative resection of disease. Patients were required to be ambulatory with a good ECOG performance status (0 or 1) prior to enrollment. XELOX therapy consisted of oxaliplatin 130 mg/m² intravenously (IV) over 2 hours on day 1 and capecitabine 1000 mg/m² orally twice a day for 14 days. Cycles were repeated every 21 days for a total of 8 cycles. FU/LV consisted of either the Mayo Clinic regimen, a rapid IV infusion of LV (20 mg/m²) followed by an IV bolus of FU (425 mg/m²) daily for five days administered every 28 days for a total of 6 cycles or the Roswell Park regimen of LV (500 mg/m² over 2 hours) and FU (500 mg/m² IV bolus during the LV infusion). This regimen was administered on day 1 of weeks 1 to 6 of an 8 week cycle for a total of 32 weeks or 4 cycles. The LV/FU regimen choice was at the discretion of the treating physician.

Results: The safety population was made up of 938 patients who received XELOX and 926 patients treated with LV/FU. The majority of adverse events occurred at a similar rate in both treatment arms. The exceptions were seen in the XELOX group which experienced more neurosensory toxicity (secondary to the oxaliplatin) and hand-foot syndrome (secondary to the capecitabine). Diarrhea, alopecia and grade 3/4 hematologic toxicities were more prevalent in the LV/FU treated patients. Treatment related mortality was 0.6% in both arms of the study.

Conclusion: The combination of oral capecitabine and IV oxaliplatin has a manageable toxicity profile in patient with stage III colorectal cancer treated in the adjuvant setting.

Managed Care Implications: Should the efficacy data prove the XELOX therapy to be equal to or better than the standard LV/FU combination, an oral agent may well replace the present standard of IV therapy in this patient population. This data should be available in the next 24 months.
**Title:** Oxaliplatin combined with weekly bolus fluorouracil and leucovorin as surgical adjuvant chemotherapy for stage II and III colon cancer: results from NSABP C-07.

**Authors:** Kuebler JP, Wieand S, O’Connell MJ, et al.


**Purpose:** Post-operative adjuvant chemotherapy has improved outcomes in patients with high-risk colon cancer. The addition of oxaliplatin to bolus and infusional fluorouracil (5-FU) and leucovorin (LV; FOLFOX4) has produced significant improvement in disease-free survival (DFS) when compared to bolus 5-FU and LV alone. The National Surgical Adjuvant Breast and Bowel Project (NSABP) initiated a similar adjuvant trial in 2000 to evaluate the addition of oxaliplatin to bolus 5-FU and LV for patients with stage II and III colon cancer.

**Methods:** Patients eligible for the trial had stage II or III colon cancer and had undergone potentially curative surgical resection with no evidence of residual disease. Surgery had to take place within 42 days of randomization. In this phase 3 trial, patients were stratified according to the institution which enrolled them and the number of metastatic regional lymph nodes found at time of surgery (0, 1-3, or ≥4). Chemotherapy consisted of one of two treatment arms. The FULV regimen, LV, 500 mg/m², over 2 hours and 5-FU 500 mg/m² as a bolus one hour into the LV infusion was administered weekly for 6 weeks followed by a 2 week rest period. Patients were to receive 3, 8-week cycles for a total duration of 24 weeks. The FLOX arm consisted of 5-FU and LV as described above in addition to oxaliplatin 85 mg/m² as a 2 hour infusion prior to the other drugs on days 1, 15 and 29 of the treatment cycle. Patients also received 3 cycles of this chemotherapy over a 6 month period of time. The primary end point of the study was DFS. Secondary end points included relapse-free survival (RFS) and toxicity.

**Results:** A total of 2,407 patients were eligible for evaluation, 1,207 treated with FULV and 1,200 with FLOX. Median follow up for patients still alive is 42.5 months. The hazard ratio for FLOX versus FULV was 0.80, which corresponds to a 20% relative risk of relapse in the FLOX treated group (P=0.0034). At four years, the overall DFS rates were 67% for FULV and 73.2% for FLOX. The percentage of patients relapse free at 4 years was 72.9% in those treated with FULV and 78.1% in those treated with FLOX (P=0.0092), again a hazard ration of 0.80 favoring FLOX. Toxicity was more severe in the oxaliplatin treatment arm. Grade 3 neurotoxicity and hospitalization for diarrhea was reported in 8.2% of FLOX patients versus 0.7% of FULV patients (P<0.001) and 5.5% of FLOX patients versus 3.0% of FULV patients (P<0.01), respectively.

**Conclusion:** The addition of oxaliplatin to a weekly dose of FU and LV significantly improves DFS in patient with stage II and III colon cancer. It can be recommended as an effective option in clinical practice.

**Managed Care Implications:** Acceptance of this dosing schedule would allow for easier, less time consuming administration of adjuvant therapy for colon cancer. Additional studies versus the FOLFOX 4 regimen and its continuous infusion of FU are warranted.

**Title:** Neurotoxicity from oxaliplatin combined with weekly bolus fluorouracil and leucovorin as surgical adjuvant chemotherapy for stage II and III colon cancer: NSABP C-07.

**Authors:** Land SR, Kopec JA, Cecchini RS, et al.


**Purpose:** The randomized, multi-center, phase 3 trial (NSABP C-07) showed a 4-year disease-free survival advantage.
for the oxaliplatin-containing regimen (FLOX) versus the non-oxaliplatin containing regimen (FULV) 72.3% versus 67.0%. Since the dose limiting toxicity of oxaliplatin is neurotoxicity, this study was designed to compare this toxicity between the two treatment arms of the study.

Methods: Four hundred (400) of the 2,492 patients enrolled in the C-07 trial were eligible to participate in the patient reported outcomes (PRO) neurotoxicity substudy. A separate protocol was developed and consent was obtained from all participants. Patients completed a Functional Assessment of Cancer Therapy (FACT)/Gynecologic Group Oxaliplatin-Specific Neurotoxicity questionnaire prior to randomization for therapy and at 4 weeks of the second treatment cycle and at 6-, 12- and 18 month follow-up visits. This instrument measured sensory symptoms (e.g. numbness and discomfort in the hands and feet), motor symptoms (e.g. general weakness, difficulty ambulating), auditory problems (e.g. buzzing/ringing in the ears) and cold-induced pain in the hands and feet. Twelve (12) of the questions formed the FACT/Gynecologic Oncology Group Oxaliplatin-Specific Neurotoxicity Scale (NTX-12). Individual responses were rated 0 (not at all), 1 (a little bit), 2 (somewhat), 3 (quite a bit), and 4 (very much) on the Likert-type scale. The scale ranged between 0 and 48 with a higher score indicating more neurotoxicity. A difference of 4 points in the NTX-12 scale was considered a minimal clinically important difference (MCID). Neurotoxicity was also assessed in all patients in the study by the treating clinician or their designee. Dose modifications were required in the study for any grade 2 toxicity that persisted between cycles or any grade 3 toxicity. Oxaliplatin was discontinued for any persistent grade 3 toxicity and any grade 4 toxicity.

Results: A total of 395 patients were eligible for the study. 206 treated with FULV and 189 with FLOX. Three participants did not complete their baseline questionnaires and two patients withdrew consent to participate in C-07 before or during therapy. The neurotoxicity questionnaire submission rates were acceptable at 78% at the 18 month interval. As expected, neurotoxicity was significantly worse in the patients treated with oxaliplatin as calculated by the mean NTX-12 scale throughout the 18-month period of the study (P=0.001). Seventeen percent of the FULV group experienced a worsening of symptoms from baseline to 6 months in comparison to 40% in the FLOX group as documented by a worsening that exceeded the MCID on the NTX-12 (P<0.0001). The percentages at 18 months were 18% and 31% (P=0.016) again favoring the FULV treated population. Patients treated with FLOX experienced significantly more hand/foot toxicity (26% vs 2.6%) and overall weakness (27.4% vs 16.2%). Interestingly enough, auditory problems were reported more frequently in the FULV treated patients. Time to resolution was also significantly longer in the oxaliplatin treated patients and continued beyond 2 years in more than 10% of the patients.

Conclusion: Oxaliplatin causes significant neurotoxicity. It is primarily experienced in the hands and feet and in some cases is long lasting.

Managed Care Implications: Improved disease-free survival with oxaliplatin-based chemotherapy in patients with colorectal cancer comes with additional toxicity. Studies will be required to investigate whether lengthening the oxaliplatin infusion, the administration of intravenous calcium and magnesium or other treatment modalities can be utilized to decrease the severity of the neurotoxicity associated with this chemotherapeutic agent.

Title: Bevacizumab (Bev) in combination with XELOX or FOLFOX4: efficacy from XELOX-NO16966, a randomized phase III trial in the first-line treatment of metastatic colorectal cancer (MCRC).

Authors: Saltz LB, Clarke S, Diaz-Rubio E, et al.


Purpose: The addition of Bev to standard 5-FU/leucovorin or irinotecan-containing chemotherapy for the treatment of MCRC has shown to improve the progression-free survival (PFS) and overall survival (OS) in a number of randomized clinical trials. This is the first phase 3 trial to evaluate the efficacy of Bev in combination with standard chemotherapeutic regimens containing oxaliplatin (XELOX or FOLFOX4) in the first-line therapy for MCRC.

Methods: A total of 1,401 patients were randomized to receive XELOX +/- Bev (Bev 7.5 mg/kg IV over 30-90 minutes on day 1; oxaliplatin 130 mg/m2 IV over 2 hours on day 1; capecitabine...
1000 mg/m² PO twice a day days 1-14 of a 21 day cycle or FOLFOX 4 +/- Bev (Bev 5 mg/kg IV over 30-90 minutes day 1; oxaliplatin 85 mg/m² IV over 2 hours day 1; leucovorin 200 mg/m² IV over 2 hours days 1 and 2; 5-FU 400 mg/m² IV bolus days 1 and 2 followed by 600 mg/m² IV by continuous infusion over 22 hours days 1 and 2 and repeated every 14 days). The study initially was a comparison of XELOX to FOLFOX4 but was modified to add either Bev or placebo once data proved the efficacy of Bev with other chemotherapeutic agents. The groups were equally matched for age, performance status and prior adjuvant therapy. The primary end point of the study was PFS with co-primary end points to evaluate whether or not Bev + chemo was superior to chemo + placebo. Efficacy was reviewed by an independent review committee.

**Results:** The median PFS for XELOX-Bev and FOLFOX4-Bev was 9.4 months versus 8.0 months for XELOX-placebo and FOLFOX4-placebo (P=0.0023; HR=0.83, a 17% reduction in relative risk). Overall response rate was not statistically different between the two groups ranging from 36-38% in the various treatment arms. There was a non-significant 0.5 months difference in time to progression between the two arms: 8.0 for patients on XELOX and 8.5 months for those on FOLFOX4, making XELOX a viable alternative to FOLFOX4. There was also no difference in the percentage of patients who developed blood clots: 1.7% in the Bev treated groups and 1.0% in the placebo treated groups.

**Conclusions:** Bev + oxaliplatin-based chemotherapy improves PFS although overall response rate is not improved. Better treatment options for patients with MCRC are needed.

**Update from the 2007 ASCO Annual Meeting**

**Title:** Randomised, double-blind multicentre phase III study of bevacizumab in combination with cisplatin and gemcitabine in chemotherapy-naive patients with advanced or recurrent non-squamous non-small cell lung cancer (NSCLC): BO17704 (The AVAiL Study).

**Authors:** Manegold C, Von Pawel J, Zatloukal P, et al.


**Purpose:** The ECOG 4599 phase 3 trial proved that the addition of bevacizumab to carboplatin/paclitaxel improved overall and progression free survival in patients with advanced NSCLC. Since the combination of cisplatin/gemcitabine is commonly used outside the US it was important to address the benefit of adding bevacizumab to this population.

**Methods:** This was a randomized, placebo-controlled phase 3 trial. The study compared two doses of bevacizumab (7.5 mg/kg or 15 mg/kg) every three weeks in combination with cisplatin (80 mg/m² IV on Day 1) and gemcitabine (1250 mg/m² IV on Days 1 and 8) versus the two chemotherapy agents plus a placebo. Chemotherapy was administered on an every three week basis. The primary end point of the study was progression-free survival (PFS). Secondary end points included overall survival (OS), response rate (RR) and safety.

**Results:** One thousand and forty three (1043) patients were randomized in the trial; 347 were treated with cisplatin and gemcitabine (control group), 345 with the same chemotherapy and 7.5 mg/kg of bevacizumab and 351 who received the chemotherapy in combination with 15 mg/kg of bevacizumab. Median PFS was 6.1 months in the cisplatin/gemcitabine arm versus 6.7 months in the 7.5 mg/kg bevacizumab and 6.5 months in the 15 mg/kg bevacizumab treatment arms. Both were statistically significant when compared to the placebo arm of the study. Although the study was not designed to compare the bevacizumab dosages, a similar treatment effect was noted between the two treatment arms. The secondary end points of response rate and safety were also reported. The response rates were 20% in the control arm of the study versus 34% in the 7.5 mg/kg bevacizumab arm and 30% in the 15 mg/kg bevacizumab arm. The authors reported no unexpected toxicity. Overall survival could not be determined due to the short duration of follow up.

**Conclusions:** Both doses of bevacizumab, 7.5 and 15 mg/kg every 3 weeks, in combination with cisplatin and gemcitabine significantly improve PFS and response rates consistent with the earlier ECOG E4599 study. No untoward toxicity was noted.

**Managed Care Implications:** Bevacizumab is effective when combined with other types of commonly used chemotherapy for the treatment of NSCLC. The most interesting finding may well be the lack of improved efficacy of the “standard” 15 mg/kg dose of bevacizumab when compared with the lower dose of 7.5 mg/kg. Although not directly compared in this study, the results none the less point to a dosing issue with bevacizumab. When seeking the lowest effective dose, 7.5 mg/kg should be chosen. Equal efficacy at one-half the standard dose would be a definite benefit in the managed care setting.
Title: Sorafenib improves survival in advanced hepatocellular carcinoma (HCC): results of a phase III randomized placebo-controlled trial.

Authors: Llovet J, Ricci S, Mazzaferro V, et al.


Purpose: HCC is the third most common cause of cancer death worldwide. Most deaths occur within 12 months of diagnosis. Presently there is no standard therapy for the treatment of the disease. Sorafenib, a multikinase inhibitor, has shown activity in a phase 2 trial.

Methods: This was a phase 3, randomized, placebo-controlled trial in which patients with advanced, measurable HCC who had received no prior systemic therapy were treated with either sorafenib 400 mg orally twice a day or placebo. The primary end points were overall survival (OS) and time to symptom progression (TTSP). Secondary end points included time to progression (TTP) and disease control rate (DCR) as defined by complete response + partial response + stable disease for at least 2 cycles. The safety of sorafenib in this patient population was also assessed.

Results: Six hundred two patients were randomized to either sorafenib (n=299) or placebo (n=303). The hazard ratio for OS (Sor/P) was 0.69 (95% CI: 0.55, 0.87; P=0.0006) and represented a 44% improvement in OS for the sorafenib-treated patients. Median OS was 10.7 versus 7.9 months, again favoring the drug therapy. Primary TTSP analysis demonstrated no significant difference between the two groups. The hazard ratio for TTP was 0.58 (95% CI: 0.45, 0.74; P=0.0000007). The median TTP was 5.5 months versus 2.8 months and the DCR was also higher (43% versus 32%) with sorafenib versus placebo. There was no difference between the groups in regards to toxicity. The study was stopped early on the recommendations of an independent drug monitoring committee.

Managed Care Implications: Based on the findings of this study, sorafenib, an oral agent, will become the therapy of choice for those patients with newly diagnosed hepatocellular carcinoma.

Title: Updated results, multivariate and subgroups analysis confirm improved activity and efficacy for FOLOFOXIRI versus FOLFOX in the G.O.N.O. randomized phase III study in metastatic colorectal cancer (MCRC).

Authors: Falcone A, Andreuccetti I, Brunetti S, et al.


Purpose: See above.

Methods: Results have been updated to a median of 36.2 months (vs 18.4 months above).

Results: The updated results confirm the significant improvements for FOLOFOXIRI in terms of response rate (60% vs 34%; P<0.001), progression-free survival (9.8 months vs 6.9 months; P<0.001) and overall survival (median 23.6 months vs 16.7 months; P=0.042) at a cost of a modest and acceptable increase in toxicity. An additional finding included an increase in the percentage of patients treated with FOLOFOXIRI able to have resection of residual metastases secondary to the effectiveness of the therapy (15% vs 6%, P=0.033; liver metastases, 36% vs 12%, P=0.017). The benefits of FOLOFOXIRI was found to be consistent across all subgroups, including those patients with unfavorable prognosis such as multiple sites of disease and liver involvement of ≥ 25%.

Conclusions: FOLOFOXIRI confirms to be the first combination to demonstrate superiority to infusional 5FU containing doublet such as FOLFIRI in terms of response rate, progression-free survival, overall survival and ability to resect residual disease. It represents a new treatment option for patients with metastatic colorectal disease.

Managed Care Implications: A 4-drug regimen +/- targeted therapy may become the standard of care for the treatment of metastatic colorectal cancer thus increasing the upfront cost of therapy. A comparison of this regimen to that of standard therapy (FOLFOX +/- targeted therapy followed by FOLFIRI +/- targeted therapy at time of progression or visa versa) will need to be evaluated.

Title: Bevacizumab (Bev) in combination with XELOX or FOLFOX4: updated efficacy results from XELOX-1/NO16966, a randomized phase III trial in first-line metastatic colorectal cancer.

Authors: Saltz L, Clarke S, Diaz-Rubio E, et al.

Purpose: The addition of Bev to oxaliplatin-based chemotherapy demonstrated a significant benefit in terms of progression-free survival (PFS) in the primary analysis (9.4 months for XELOX or FOLFOX+Bev versus 8.0 months for XELOX or FOLFOX + placebo; P=0.0023) or when PFS was assessed by an independent review committee (11.1 months vs 8.6 months; P<0.0001). Median follow-up for survival in now at 18.6 months and results will be presented at the June meeting in Chicago.

Conclusions: This large international phase 3 trial continues to demonstrate that the addition of BEV to oxaliplatin-based chemotherapy significantly improves PFS.

Managed Care Implications: Bev has proven to be essential in the treatment of first-line metastatic colorectal cancer when combined with an oxaliplatin-containing regimen. Oral capecitabine may replace the use of intravenous 5FU and leucovorin in patients with this disease.

Title: Final Results of OPTIMOX2, a large randomized phase II study of maintenance therapy or chemotherapy-free intervals (CFI) after FOLFOX in patients with metastatic colorectal cancer (MCR): A GERCOR study.


Purpose: The OPTIMOX2 study was designed to evaluate the value of stopping chemotherapy after 6 bimonthly cycles of FOLFOX.

Methods: Patients were randomized to OPTIMOX1, 6 cycles of FOLFOX7 followed by 5FU and leucovorin until progression then reintroduction of FOLFOX7 or OPTIMOX2, 6 cycles of FOLFOX7 followed by no chemotherapy with reintroduction of FOLFOX7 before tumor progression reached baseline measurements.

Results: Two hundred and two (202) patients were randomized on the study. Response rates, complete + partial responses, were 63% for OPTIMOX1 and 61% for OPTIMOX2 which is not statistically significant. Median progression-free survival (PFS) was 8.3 months for OPTIMOX1 and 6.7 months for OPTIMOX2 (P=0.04). Median duration of disease control (addition of PFS of first FOLFOX7 administration + PFS of FOLFOX reintroduction if no progression at first evaluation) was 10.8 months in the OPTIMOX1 arm and 9.0 months in the OPTIMOX2 arm (P=0.32). Median duration of CFI in the OPTIMOX2 arm was 4.6 months. Median overall survival was 24.6 months in those patients treated with OPTIMOX1 and 18.9 months with OPTIMOX2 (P=0.05).

Conclusions: Maintenance LV5FU can prolong PFS and OS especially in patients with poor prognosis. CFI can only be recommended in patients without these prognostic factors.

Managed Care Implications: A subset of identifiable patients will benefit from CFI thus decreasing overall drug spend and decreasing patient exposure to the toxicities associated with the treatment of metastatic colorectal cancer.

Dr. Mucenski is the Director of Pharmacy Operations for UMPC Cancer Centers.

Industry Thought Leaders
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MCO: What concerns to employer groups have regarding the cost of the new pipeline of emerging cancer drugs?

Dr Sherman: When it comes to employer group opinions on cancer treatment costs, there are two ends of the spectrum. On one end, the employer groups view cancer as a catastrophic condition that should be taken care of by using the health benefit dollars allocated for all their employees. The majority of employer groups seem to fall into this category, supporting care of the catastrophic conditions. On the other end of the spectrum, a few employer groups feel that employees with high cost medical needs should cover a larger percentage of the cost on their own. At Regence, we always ask, "What's driving the employer's philosophy?" "Are there limited financial resources?" In the cases where it’s cost that’s influencing the decision, we’re seeing more and more employer groups evaluating putting high cost medications on a separate tier with higher contributions. Since the medications that we embrace at Regence are likely to have high value because of the stringent evidence-based review we perform, we try to guide them through that decision by showing them the pros and cons of benefit options. An explanation of our evidence-based review and the outcomes of that process is typically enough to dissuade employer groups from segregating medications solely based on cost.